ATTACHMENT 1

# STATEMENT OF WORK

# FOR THE CONDUCT OF STUDIES TO EVALUATE

# THE TOXIC AND CARCINOGENIC POTENTIAL

# OF TEST ARTICLES IN LABORATORY ANIMALS

# FOR THE NATIONAL TOXICOLOGY PROGRAM (NTP)

**August, 2004**

# TABLE OF CONTENTS


I. GENERAL PROJECT OBJECTIVES 1

II. PROJECT MANAGEMENT 2

III. GENERAL STUDY DESIGNS 2

IV. GOVERNMENT FURNISHED MATERIALS 3

V. INSTRUCTIONS FOR PREPARATION OF TECHNICAL AND BUSINESS PROPOSALS 3

VI. GENERAL REPORTING REQUIREMENTS 3

A. PERIODIC REPORTS 3

B. STUDY REPORTS 4

C. OTHER REPORTS 4

D. DELIVERY TERMS 4

E. TRACKING SYSTEM 4

F. PUBLICATION OF RESEARCH RESULTS 5

APPENDICES TO THE SOW

A. STUDIES OF GREEN TEA EXTRACT BY GAVAGE

B. STUDIES OF ANNATTO EXTRACT BY DOSED FEED

C. STUDIES OF SODIUM TUNGSTATE DIHYDRATE BY DOSED WATER

D. STUDIES OF 5-AMINO-O-CRESOL BY DERMAL EXPOSURE

E. SCHEDULE FOR WORK ASSIGNMENTS

F. SCHEDULE FOR OPTIONAL WORK ASSIGNMENTS

**STATEMENT OF WORK**

**FOR THE CONDUCT OF STUDIES**

**TO EVALUATE THE TOXIC AND CARCINOGENIC POTENTIAL**

**OF TEST ARTICLES**

**IN LABORATORY ANIMALS**

**FOR THE NATIONAL TOXICOLOGY PROGRAM (NTP)**

## I. GENERAL PROJECT OBJECTIVES

The National Toxicology Program (NTP) is responsible for evaluating the toxic and carcinogenic potential of environmental agents that may pose a health hazard to citizens of the United States. The purpose of this contract is to conduct short-term and long-term studies of a variety of test articles by various routes of exposure. The project is designed to study diverse agents that may include: food additives, colorants or flavorings; pharmaceuticals and herbal remedies; herbicides, fungicides, and pesticides; ingredients found in soaps, lotions, perfumes, and cosmetics; in detergents and cleaners; in a wide variety of consumer products; used in manufacturing, or industrial settings, etc.

The Government anticipates that studies of these test articles will be conducted approximately as follows: Three (3) test article study starts in fiscal year 2005 and four (4) test article study starts each year in fiscal years 2006 through 2010. Study Starts (including prestart efforts) will begin once a test article is identified and shipped to the contractor and may go on to include any but not necessarily all of the following: 14-day, 13-week and 2-year studies. The Government may unilaterally exercise its option to conduct studies of one additional test article each year in years one (1) through six (6) of the contract. The contractor shall prepare and submit the study-specific and other reports set forth in each individual chemical-specific Statement of Work, according to the formats specified in the NTP Specifications.

Study designs will be provided for individual test articles along with a Schedule of Milestones and Deliverables. Four Sample Work Assignments are provided, representing various routes of exposure, to determine contractor capabilities and to standardize costing by offerors. However, the type and number of studies to be conducted under this contract during each year may vary from the sample Work Assignments and projected schedule provided here.

Independently, and not as an agent of the Government, the contractor is to furnish all the necessary services, qualified personnel, materials, equipment and facilities not otherwise provided by the Government as needed to perform the work set forth below.

All studies are to be conducted according to the requirements described in Attachment 2: Specifications for the Conduct of Studies to Evaluate the Toxic and Carcinogenic Potential of Chemical, Biological and Physical Agents in Laboratory Animals for the National Toxicology Program. Work is to be performed in accordance with the Good Laboratory Practice Regulations established by the FDA for Non-clinical Laboratory Studies (Fed. Register, Vol 52, # 172, Friday September 4, 1987, pp 33768-33782; 21 CFR Part 58).

## II. PROJECT MANAGEMENT

This contract will be managed on a "Work Assignment" basis, with individual Work Assignments prepared for each test article or group of articles to be studied under the contract. Each Work Assignment will be initiated by the Project Officer, will include a detailed description of the work to be performed, and will be sent directly to the Contractor. The Contractor will be asked to submit a technical proposal to include a description of how the work will be conducted. This proposal is only to include those details specific for the proposed Work Assignment and not generic procedures previously provided in the original proposal submitted at the time of contract award. In addition, a cost proposal is to be submitted itemizing the resources needed (labor hours, materials and supplies, subcontract costs, overhead, fringe benefits, G&A, fee, etc.) for that Work Assignment. These proposals are to be submitted to the Contracting Officer and Project Officer for review, generally within 3-5 weeks from receipt of the Work Assignment. The Contractor may not proceed until they receive an approved, signed "Initiation" Work Assignment from NIEHS and sign and return the Work Assignment to the Contracting Officer.

Once approval of the Work Assignment has been received, prestart activities (Phase 1) may begin, such as bulk chemical reanalysis, validation of dose formulation and analysis methods, proficiency studies for special assays, etc. Such Phase 1 activities and resulting reports will be reviewed and approved prior to the start of subsequent Phases.

During the course of the studies, if modifications are needed, a "Revised" Work Assignment will be sent by the Contracting Officer to the Contractor for signature. If modifications are extensive, a cost proposal may be requested prior to NIEHS signing and approving the "Revised" Work Assignment.

It should also be noted that work within each Work Assignment may be divided into optional phases, with the option for each phase exercised independently.

Within 60 days of completion of all work required under a Work Assignment, the Contractor will submit a "Completion" Work Assignment indicating that all deliverables have been submitted and providing a final accounting of all costs expended in the completion of the work required under the Work Assignment.

IMPORTANT NOTE: Once the contract is awarded, vouchers submitted for a Work Assignment are to include the cumulative amount spent for the Work Assignment during the reporting period, as well as separate costs incurred for each phase within the Work Assignment.

## III. GENERAL STUDY DESIGNS

The design of actual studies will vary as needed depending on the individual test articles, route(s) of exposure, and endpoints to be evaluated. Study duration may be from a few days up to 2-years or lifetime; exposure may begin *in utero* or in young animals; the route of administration may be dosed feed, dosed water, gavage, dermal, parenteral (intraperitoneal, subcutaneous, intravenous, intratracheal).

Evaluations may include the following:

- the characterization of the bulk material (identity and purity)
- validation of dose formulation and analysis methods
- in-life chemistry activities during these studies include periodic bulk chemical reanalysis; monthly dose formulations and periodic dose analyses
- other in-life activities may include clinical observations; body weights; food or water consumption if appropriate
- at sacrifice, organ weights, necropsies, histopathology; cell proliferation (BrDU or PCNA);

collection of frozen tissues for oncogenes
- other endpoints may include measurement of cytochrome P450s, glutathione, alpha-2μ-globulin; clinical pathology (hematology, clinical chemistries, urinalysis, thyroid hormones, methemoglobin, clotting time, and others); sperm and vaginal cytology evaluations; immunotoxicity measurements (involves only collection and shipment of samples to an NIEHS contractor for evaluation); FOB; teratology assessments.

Details for typical 14-day, 13-week, 26/39-week and 2-year studies and specific requirements for individual routes of administration may be found in the NTP Specifications.

## IV. GOVERNMENT FURNISHED MATERIALS

- test articles (unless specified otherwise)
- methods for test article characterization – identity and purity (unless specified otherwise)
- methods for dose formulation and dose analysis
- F344 rats and B6C3F1 mice
- TDMS equipment, software and user manuals
- serology testing by an NTP contractor for animal disease screening.

## V. INSTRUCTIONS FOR PREPARATION OF TECHNICAL AND BUSINESS PROPOSALS

Four Sample Work Assignments (A, B, C, and D) have been included in Attachment 1, the Statement of work, to provide offerors some examples of study designs that might be conducted under this contract. Offerors are to provide technical and cost information in their proposal for each of the Sample Work Assignments.

Base Contract: The Government anticipates that studies of test articles will be conducted approximately as follows: Three (3) test article study starts in fiscal year 2005 and four (4) test article study starts each year in fiscal years 2006 through 2010. For estimating the total effort and costs for the 10-year period of this contract, offerors are to assume Work Assignments according to APPENDIX E: Schedule for Work Assignments, of Attachment 1, the Statement of Work, for the base contract.

Options: The Government may unilaterally exercise its option to conduct studies of one (1) additional test article each year in years one (1) through six (6) of the contract. For costing purposes, offerors are to assume the study type (13-week and 104-week gavage) and the schedule provided in APPENDIX F: Schedule for Optional Work Assignments, of Attachment 1, the Statement of Work for calculating costs and effort for these optional studies.

## VI. GENERAL REPORTING RQUIREMENTS

### A. PERIODIC REPORTS

1. Monthly Progress Report

   A Monthly Progress Report shall be mailed by the fifteenth day of each month. Each Monthly Progress Report shall be submitted in the format specified in the NTP Specifications. No QAU audit of this progress report is required.

2. Sanitization Methods Report

   A Sanitization Methods Report shall be due 90 days after contract award and shall describe in detail:

a. The methods being used (and/or proposed for future use) for sanitization of equipment used in the studies to include at least cages, racks, feeders, watering devices, magnetic field generating system, rooms, walls, halls and buildings. Describe methods in detail, including commercial products used, their EPA registration number and their chemical constituents if possible. Include any change made in procedure or products used in the appropriate Monthly Progress Report.

b. The methods in use to keep animal quarters free of insects and other vermin. Again, specify commercial products used, EPA registration number and their chemical constituents, if possible. Report any changes in procedures or products used in the appropriate Monthly Progress Report.

3. Water Analysis

Water samples shall be collected for analysis and a report of the results submitted to the NTP at least once per year. An analysis is required during the in-life portion of the 13-week study and once each year during the two-year study. For laboratories that are not currently conducting studies for NTP, a report shall also be submitted within 30 days of contract award.

4. Health and Safety Chemical Hygiene Plan (General Facility Plan)

An NTP approved Health and Safety Plan is required prior to any work commencing under the contract. An updated Health and Safety plan shall be submitted to the NTP for review and approval every two years and anytime it is modified. Action to correct deficiencies shall be taken within 30 days of notification that such action is required.

B. STUDY REPORTS

Study Reports will follow the Report Formats provided in the NTP Specifications and be submitted according to the Schedule for Milestones and Deliverables included in each Work Assignment.

C. OTHER REPORTS

Any incident or unforeseeable occurrences not listed in this document, or any physical modifications to the laboratory facilities, as well as any changes in personnel which might have an impact on the conduct and results of the studies shall be reported immediately to the NTP.

D. DELIVERY TERMS

All deliverables required by this Statement of Work shall be delivered f.o.b. destination in accordance with the NTP Specifications and by the dates specified within each Work Assignment.

E. TRACKING SYSTEM

For the purpose of tracking progress during a Work Assignment, the contractor shall utilize Chemical Status Reports (CSR) containing milestones for the studies under this contract, including all special studies (i.e. toxicokinetics, hematology, clinical chemistries, etc.). Progress with reference to this CSR shall be reported to the Project Officer and adjustments made as required by the Project Officer monthly. Any change affecting the final due date of a prechronic or two-year report must be approved by the NTP Contracting Officer.

F. PUBLICATION OF RESEARCH RESULTS

It is anticipated that the results of research conducted under the Contract shall be published in the peer reviewed scientific literature. Specific details concerning authorship and technical issues surrounding the publication of the research shall be discussed and agreed upon by the Principal Investigator and the NIEHS Project Officer on a case-by-case basis.

Because premature release of information developed under the contract could be harmful to the public, the Contractor and the Government agree that it is important to consider issues related to the timing of the release of research results when submitting information for publication. With regard to public disclosures of the research to be carried out pursuant to this contract, the Contractor agrees to submit all proposed articles to the Project Officer at least thirty (30) days in advance of submission for publication. Within this thirty-day period the Contracting Officer shall inform the Contractor if there are serious concerns raised by the timing of said publication.

Upon receipt of a notification that the Government objects to the publication of said information, the Contractor agrees to withhold submission of said publication for an additional thirty (30) days while the author and the Project Officer discuss the issues raised by the Contracting Officer's notification. The Contractor agrees to give good faith consideration to all such issues and further agrees that it will not knowingly submit for publication any article, abstract or other item which would be harmful to the public welfare; however, the final decision on whether to submit an article for publication shall rest with the author of said publication after the procedures set forth above are followed. Similar procedures shall apply for scientific presentations and meeting abstracts.